compositions of applicants' invention, having been lyophilized, contain channels vacated by water that has been frozen and dried. The end product of this process is quite different from that of a tabletting process, which is compressed and dry, without the channeled structure and interstitial spaces available in a lyophilized composition's structure.

The Office Action of December 6, 2002 objected to claim 56 as being a substantial duplicate of claim 1. Should claim 1 be allowed, applicants will determine whether to cancel claim 56.

The Office Action rejected claims 27 and 65 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection was: "the term 'vegetable protein derivatives' in claims 27 (line 2), 65 (part(b)(i)) is vague and indefinite, as it is not clear what compounds are encompassed by this phrase..." [Office Action of 12/6/03, p. 3]. Applicants respectfully request reconsideration of this rejection in view of the ensuing discussion.

Applicants respectfully direct the Patent Office's attention to the Specification at page 5, lines 28-30, which read as follows:

> Suitable matrix forming agents include, but are not limited to, animal and vegetable protein derivatives, such as gelatins, dextrins, soy, and wheat [and] psyllium see proteins...[Specification, p. 5, l. 28-30]

Applicants respectfully submit that the foregoing would be sufficient for one of ordinary skill in the art to understand the nature of the phrase "vegetable protein derivatives". Applicants respectfully request reconsideration of the foregoing rejection in light of this discussion.

The Office Action of December 6, 2002 rejected claims 1, 2, 6-9, 13-15, 19-20, 22, 24-29, 37, 45-56, 49-53, 56-60, 63 and 65 under 35 U.S.C. §102(b) as being anticipated by Huber (U.S. Patent No. 4,122,157). Applicants respectfully request reconsideration of this rejection in view of the ensuing discussion.

The basis for this rejection was as follows:

> Huber teaches nitrofurantoin sustained release tablets. Exemplified is a tablet comprising a rapid release layer and a slow release layer, wherein the rapid release layer comprises 33% nitrofurantoin and 67% in rt pharmaceutical excipients, and the slow release layer comprises 36% nitrofurantoin, 31% hydroxypropylmethylcellulose, and 33% inert pharmaceutical excipients...Thus, Huber and the instant invention both teach composition comprising a sustained release layer and a fast release

> layer, wherein the slow release layer comprises 31% of a water-soluble polymer (hydroxypropylmethylcellulose), hydrogenated vegetable oil and 36% of an active agent (nitrofurantoin), and the fast release layer comprises matrix forming agents (binders, such as gelatin and starch), and 33% of an active agent (nitrofurantoin). [Office Action of 12/6/03, p. 4]

As applicants have earlier pointed out, the Huber reference describes ***compressed oral*** tablets having:

> ***two discrete portions***, a rapid release portion and a slow release portion, each portion containing a specific quantity of specially prepared nitrofurantoin. Still more particularly, the present invention relates to ***a compressed pharmaceutical tablet***. [Huber, col. 1, l. 47-65] (emphasis added)

Thus, Huber relates to a ***compressed*** tablet suitable for ***oral*** administration having ***two discrete portions***. While the Office Action contends that the mention of the distinction between the end products of compression and freeze-drying processes is not persuasive, in fact, the structure of a compressed tablet and a freeze-dried composition are quite different. A tablet is completely solid in form, with a compressed volume. In contrast, a freeze-dried structure is porous and maintains the volume of the original liquid composition from which it is derived. A tablet requires a means to enable dissolution, such as a polymer, whereas a freeze-dried product contains channels through which water can flow, enabling dissolution at the desired rate. Thus, the presence of the description of the claimed composition as "freeze-dried" would indicate to one of ordinary skill in the art that the structure of that composition is quite distinct from that of a compressed tablet. In view of this distinction, because Huber does not describe or suggest a lyophilized composition, nor a composition capable of being lyophilized without cracking or disintegration, applicants respectfully request reconsideration of the rejection under 35 U.S.C. §102(b).

The Office Action of December 6, 2003 further rejected claims 1-2, 6, 7-10, 13-27, 29, 37-38, 41-43, 45-47, 49-53, and 56-67 under 35 U.S.C. §103(a) as being unpatentable over Saslawski et al. (WO 99/33448). Applicants respectfully request reconsideration of this rejection in view of the ensuing discussion.

The Saslawski et al. reference relates, as does Huber, to ***a compressed tablet***. In the case of Saslawski et al., the tablet is a bilayer tablet "comprising at least two superposed layers,

characterized in that: a first outer layer is composed of a mixture of excipients and of a first active substance...the second layer, arranged in contact with the said first layer, consists of a nonbiodegradable, inert porous polymeric matrix in which a second active substance is dispersed." [Saslawski, p. 1, Abstract]. Thus, the Saslawski tablet contains an outer layer and an inner layer that are ***compressed*** [Saslawski, p. 21, l. 19-35]. As with the other compressed tablet structures, that of Saslawski does not have the channeled structure of a lyophilized product, nor could it be freeze-dried as it has no water present in the structure. Again, there are considerable structural differences between a compressed tablet and the freeze-dried compositions of applicants' invention, as set forth above. Saslawski et al. neither suggests nor describes a freeze-dried composition nor a combination of any freeze-dried layer with another layer to attain a dual-rate release composition.

Moreover, Saslawski et al. contemplates a "prolonged release layer" containing "inert" materials (Saslawski et al., p. 12, l. 3-11) rather than water soluble polymers as in the compositions of applicants' invention (Specification, p. 5, l. 3-6). Saslawski et al. clearly describes compressing and drying their compositions for form compressed tablets, in contrast to the compositions of applicants' invention (Saslawski et al., p. 15, l. 15-37). Applicants therefore respectfully request reconsideration of the aforementioned rejection over Saslawski et al.

The Office Action further rejected claims 12 and 40 under 35 U.S.C. §103(a) as being unpatentable over Saslawski et al. and further in view of Morella et al. (U.S. Patent No. 5,378,474). Claims 10, 12, 38 and 40 were also rejected under 35 U.S.C. §103(a) as being unpatentable over Huber et al. and further in view of Morella et al. Applicants respectfully request reconsideration of these rejections in view of the ensuing remarks.

These rejections were based upon the same reasoning as set forth above vis-à-vis claims 1-2, 6, 7-10, 13-27, 29, 37-38, 41-43, 45-47, 49-53 and 56-67. Morella et al., contends the Office Action, "teaches sustained release pharmaceutical compositions having a core element and a core coating. Antibiotics disclosed for use as active agents include nitrofurantoin and metronidazole." [Office Action of 12/6/03, p. 6]

Morella et al., as does Saslawski et al. and Huber et al., relates to an oral tablet for sustained release via stomach digestion. Morella's tablet contains an ***inner core and an outer coating***; the coating is formulated specifically for fast dissolution, but nowhere does it indicate that the outer coating should be utilized for fast release of drug. Furthermore, the components of the Morella et al. product are specifically dried [col. 13, l. 1-3], precluding the product's being subject to freeze-drying and lyophilization. Thus, its structure is similar to that of Saslawski et al. and Huber: a dry, compressed tablet. Even in combination with Saslawski et al. or Huber et al., one of ordinary skill in the art would not have reached the compositions of applicants' invention based upon Morella et al. because neither describes a product that is suitable for freeze-drying nor does either suggest such a product. As set forth above, the resulting compositions are quite different structurally. Creating a freeze-dried structure having fast-release and slow-release components is not easy to achieve. Nothing in Saslawski et al., Huber et al. or Morella et al. would direct one of ordinary skill in the art to do so. All refer to dry, compressed tablet compositions. Thus, applicants respectfully request reconsideration of these rejections.

Claims 28, 33-35, 36 and 44 were rejected under 35 U.S.C. §103(a) as being unpatentable over Saslawski et al. and further in view of Gole et al. (U.S. Patent No. 5,558,880). This rejection over the combination of Saslawski et al. and Gole was based upon Gole et al.'s contended teaching of:

> ...pharmaceutical dosage forms defined by a matrix containing gelatin, pectin and one or more amino acids having from about 2 to 12 carbon atoms...It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the matrix of Gole et al. to the immediate-release granule of Saslawski et al. because a) Gole et al. and Saslawski et al. are both directed to pharmaceuticals that provide immediate release of an active agent; b) Saslawski et al. teach many of the matrix components of Gole et al. as disintegrating agents for use in their immediate release layer; c) Gole et al. his matrices as resisting disintegration under manufacturing and handling, and as exhibiting a fast speed of dissolution upon ingestion; thus, one of skill in the art would be motivated to add the matrix of Gole et al. to the immediate release granule of Saslawski et al. because of the expectation of producing a tablet that resists disintegration under manufacturing and handling and exhibits a fast speed of dissolution upon ingestion." [Office Action of 12/6/03, pp. 7-8]

Claims 33-35, 36, 41-44, 64, 66 and 67 were also rejected under 35 U.S.C. §103(a) as being unpatentable over Huber et al. and further in view of Gole et al. The Office Action adds that the Huber et al. reference lacks matrix agents consisting of gelatin, xanthan gum and amino acids. Applicants respectfully request reconsideration of the foregoing rejections in view of the ensuing discussion.

Gole et al. relates to a solid freeze-dried dosage form that dissolves quickly [col. 2, l. 39-45 and 54-55] and a method for making such a dosage form. Gole et al. describes homogeneous dosage forms and nowhere suggests or describes the use of such quickly dissolving compositions in combination with another, sustained release layer. Nowhere does Gole et al. motivate one of ordinary skill in the art to combine its teachings with Saslawski et al., Huber or Morella et al. in order to reach the compositions of applicants' invention.

Nowhere do any of the cited patents describe or suggest the combination of compressed tablets and lyophilized materials. It is not clear that such a combination would even by physically possible, given that compressed tablets have no water available for the freeze-drying process. Furthermore, even combining such products would still not direct one of ordinary skill in the art to the compositions of applicants' invention, which are lyophilized and can even, surprisingly, be a uniform mixture of slow and fast release phases.

Even if it were possible to place the freeze-dried compositions of Gole et al. on a compressed tablet such as described in Saslawski et al. or Huber et al., the freeze-dried structure would not be able to withstand the force of compression. Furthermore, if it were to be compressed, the release rate of drug in the composition would decrease because the channels created by the freeze-drying process would cease to exist once crushed. Moreover, the ingredients used in a tablet composition may not be capable of being subjected to the freeze-drying process as the process may affect the materials therein and change their properties.

Gole et al., Huber et al. and Saslawski et al. all describe at least one means of achieving a fast-dissolving composition (although Gole et al. describes a homogenous compositions rather than multiple layers or phases). Why would one of ordinary skill in the art combine a freeze-dried fast-release composition with a bilayer compressed tablet that already has a fast-release layer? Applicants respectfully contend that

such a combination would not be suggested or described in the foregoing patents. Therefore, applicants respectfully request reconsideration of these rejections.

Claims 16-18, 21, 23, 47 and 61-62 were rejected under 35 U.S.C. §103(a) as being unpatentable over Huber et al. and Saslawski et al. on the ground that:

> it would have been obvious to one of ordinary skill in the rat at the time the invention was made to incorporate the percent weights of fatty acids and active agents taught by Saslawski et al. into the invention of Huber et al. because a) both Saslawski et al. and Huber et al. teach sustained release tablets comprising a sustained release layer comprising a water-soluble polymer and an active agent and a fast release layer comprising a matrix forming agent and an active agent; and b) it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233. [Office Action of 12/6/03, pp. 9-10]

Applicants respectfully request reconsideration of the foregoing rejection in light of the ensuing remarks.

Applicants respectfully point out that both Huber et al. and Saslawski et al., as discussed above, relate to compressed tablets. Even if one of ordinary skill in the art were to create a bilayer tablet as set forth in Huber et al. and Saslawski et al., the resulting product would be a **compressed tablet**, not a freeze-dried composition. The tablet would not have the same volume as that of the original liquid material from which the composition was made; it would not have channels created by the removal of water from the product. It would be quite different in form and function from a compressed tablet.

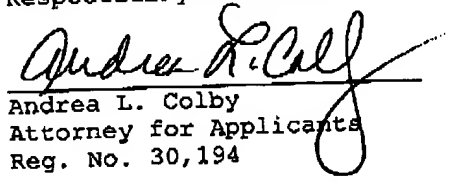
Nowhere in Huber et al. or Saslawski et al. do the patents suggest or describe multi-layer compositions having freeze-dried structures.

Moreover, the applicability of the *In re Aller* case is limited in this situation because the freeze-dried compositions of applicants' invention are not simply "optimized" versions of the Huber et al. and/or Saslawski et al. patents. Rather, they are different in form and function in that their structures preserve the volume of the product without compression and maintain a two-phase, sustained-release composition that neither patent suggested or described. Applicants therefore respectfully request reconsideration of this rejection in view of the foregoing discussion.

Applicants therefore request reconsideration of the rejection of the claims under 35 U.S.C. 103(a) over Huber in view of Morella et al., Conte et al., Saslawski et al. and Gole et al.

In view of the foregoing discussion, applicants respectfully request reconsideration of the rejections set forth in the Office Action of December 6, 2002. An early allowance is earnestly solicited.

Respectfully submitted,



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